SYSTEM FOR THE CONTROL, VERIFICATION AND RECORDING OF THE PERFORMANCE OF A RADIOISOTOPE GENERATOR'S OPERATIONS

RELATED U.S. APPLICATIONS

Not applicable.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

Not applicable.

REFERENCE TO MICROFICHE APPENDIX

Not applicable.

FIELD OF THE INVENTION

[0001] This invention relates to a system that allows the control, verification and recording (logging) of the performance of all operations carried out by a radioisotope generator. Such system comprises one or more sensors connected to an electronic device for data processing to provide performance control of a radioisotope generator, such as a Mo-99/Tc-99m Generator. In particular, the invention refers to a digitalized system for the measurement, verification and logging of all the operations performed by a Mo-99 /-Tc-99m generator, including an electronic sensor of the elution of the generator, an eluted activity measurement device, a nuclear quality control device for Tc-99m, a communication interface to an electronic data processor and an user interface program.

BACKGROUND OF THE INVENTION

[0002] Although technical bibliography and literature provides for a great variety of Tc-99m generators, there is no knowledge of digital generators including digitalized equipment to control, verify and log every operation performed by the generator through a simple and economical means

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such as a conventional computer connected to suitable means of sensing and with the appropriate software to process the information obtained through such sensors.

[0003] For example, improvements may be cited that comprise the generator of Technetium disclosed in the United States Patent No. 5,774,782 referred to a .sup.99 Mo/.sup.99m *Tc* generator system including a sorbent column loaded with a composition containing .sup.99 Mo. The sorbent column has an effluent end in fluid communication with an anion-exchange column for concentrating .sup.99m *Tc* eluted from the sorbent column. A method of preparing a concentrated solution of .sup.99m *Tc* includes the general steps of:

   a. providing a sorbent column loaded with a composition containing .sup.99 Mo, the sorbent column having an effluent end in fluid communication with an anion-exchange column;

   b. eluting the sorbent column with a salt solution to elute .sup.99m *Tc* from the sorbent and to trap and concentrate the eluted .sup.99m *Tc* on the ion-exchange column; and

   c. eluting the concentrated .sup.99m *Tc* from the ion-exchange column with a solution comprising a reductive complexing agent.

[0004] Moreover, U.S. Patent No. 4,782,231 discloses a standard component .sup.99m *TC* elution generator useful for medical purposes and consisting of prefabricated component parts. The main generator column of the device may be used both as an irradiation container and an elution container, enabling the user to supply activated or no activated parts. The main generator column made from by neutrons little activable materials serves first as reactor irradiation ampoule and after having been activated in the reactor by neutrons and after a simple adjustment serves directly as the generator column. It is filled with water insoluble molybdates or polymolybdates (with the molybdenum content in the range 10-40%), easily releasing .sup.99m *Tc* generated by radioactive decay of the mother

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.sup.99 Mo formed in it by neutron activation. This column filling serves originally as target material for reactor irradiations and afterwards it is directly used as the generator elution matrix.

[0005] U.S. Patent No. 4,837,110 discloses a technetium-99m generator, its preparation and its use wherein silica gels modified with amino groups or magnesium silicates are suitable carrier materials for technetium-99m generators since they retain copper(II) ions well and thus produce a copper-free elute.

[0006] U.S. Patent No. 4,280,053 describes a Technetium-99m generator has a matrix having a compound of molybdenum-99 bound into or forming the matrix, the compound of the molybdenum-99 being substantially insoluble in an eluant which can be used in a radiopharmaceutical and the molybdenum compound permitting diffusion of technetium-99m therethrough and elution therefrom. The molybdenum compound can be a monomolybdate, an isopolymolybdate or a heteropolymolybdate and zirconium molybdate is preferred although other cation molybdates may be used. Methods of preparation of the generator include dissolving irradiated molybdenum trioxide in alkaline solution and precipitating the molybdate at a selected pH and packing the precipitate in finely divided form into a column.

[0007] None of the above mentioned generators embrace an equipment like the one described below, including novel features and performing new functions.

[0008] The proposed system subject of this invention, when incorporated to a radioisotope generator, substantially enhances its general usefulness and mainly adds previously unknown features to it.

BRIEF SUMMARY OF THE INVENTION

[0009] Summarizing, this invention refers to a digital technetium Tc-99m generator obtained by incorporating devices to allow the control, verification and recording of all the operations performed by the generator, comprising:

- a conventional traditional generator Mo-99/Tc-99m, using either a dry or wet column, such as the ones commercially available for use in nuclear medicine;

- an electronic sensor of elution;

- an eluted activity measurement sensor;

- a device to measure the nuclear quality of the eluted Tc-99m;

- an electronic memory means with information to the user regarding: Generator No., Lot No., activity, calibration and expiration dates;

- a communication interface, whether via RS232; USB, parallel Port or any other input-output port of a PC; and

- a control and user interface software.

[0010] The applicability of these improvements provides the following advantages:

- it allows the user to know the activity available in the generator at a any given time without having to resort to tables or to recall the last elution conducted on the generator, especially when generator elutions are conducted by more than one technical personnel;

- it automatically logs the day and hour of elution, saving it in an electronic file; records the eluted activity and the identification of the operator;

- it automatically measures the activity of the eluted Tc-99m and determines its nuclear purity (μCi Mo-99 per mCi Tc-99m);

- it computes the specific activity of Tc-99m which is important to determine the suitability of an eluate for labeling some radiopharmaceuticals, such as ECD and others known to those skilled in the art;

- in the case of the dry Mo-99/Tc-99m generator, the information regarding the residual humidity of the generator is fundamental to secure the next elution, since the elution performance drops drastically in case the generator remains "wet". The system guides the user to resolve the problem. If the user fails to log the solution, the producer may remotely access the data and call the user to help in resolving the problem;

- the log system records the operations conducted on all the generators for the operator´s review;

- the log system allows conducting statistical analysis on the use of Tc-99m by the Nuclear Medicine Unit; and

- the software, herein called "watchdog", is an integral part of this invention and alerts the operator in case of possible unauthorized elutions.

[0011] These are only some of the significant advantages of the present invention that will become apparent upon reading the following description and upon reference to the enclosed drawings.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0012] Figure 1 is a schematic view of the generator's connection to the PC, either directly or through a port RS232, USB, Parallel, etc.

[0013] Figure 2 shows a schematic view of an embodiment of the proposed elution detection sensor, where the elution detection is conducted by conductometry, which is based on the measurement of the electrical resistance of a portion of a metal tubing through which the physiological solution or the elution passes.

[0014] Figure 3 is another schematic view of another embodiment, wherein the sensor detects the elution by measuring the changes in the intensity of a light beam which passes through a translucid section of the elution tubing.

[0015] Figure 4 is a schematic view of still another embodiment, wherein the sensor detects the elution by impedanceometry based on measuring the changes in the frequency of a free oscillator.

[0016] Figure 5 shows a schematic view of another embodiment, wherein the sensor detects the elution by measuring the changes in capacity in the elution as the eluate flows through the elution tubing.

[0017] Figure 6 shows a schematic view of a further embodiment, wherein the sensor detects the elution by measuring the changes in radioactivity emitted by the eluate as it passes through the elution tubing.

[0018] Figure 7 shows another schematic view of an embodiment, wherein the sensor detects the elution based on the magnet-hydrodynamic principle, i.e. the measurement of the weak orthogonal electric field created to the magnetic field applied to the elution tubing.

[0019] Figure 8 shows a schematic view of a circuit number 1 of the identification loop for taking knowledge to the program that the circuit is connected to the port.

[0020] Figure 9 shows the schematic view of the circuit number 2, working in similar form to the previous one but loads the capacitor whose load is checked by DCD port.

[0021] Figure 10 shows a schematic view of a circuit number 3, which works by circulation of alternate current.

[0022] Figure 11 shows another schematic view of a circuit number 4, which actuates by changes in light intensity.

[0023] Figure 12 shows a schematic view of circuit number 5 for the RadioFarma Elutec II system.

[0024] Figure 13 shows a schematic view of circuit number 6 for the RadioFarma Elutec III.

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DETAILED DESCRIPTION OF THE INVENTION
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[0025] This invention refers to a system that, when incorporated to a radioisotope generator performs certain operations which enhances its general usefulness. The systems comprises:

- a conventional traditional generator Mo-99/Tc-99m, using either a dry or wet column, such as the ones commercially available for over 40 years in Nuclear Medicine;

- an electronic sensor of elution;

- an eluted activity measurement sensor;

- a device to measure the nuclear quality of the eluted Tc-99m;

-an electronic memory with information to the userregarding: Generator No., Lot No., activity, calibration and expiration dates;

- a communication interface via RS 232; USB, parallel Port or any other input-output port of a PC. By PC it should be understood desktop PC, notebook PC, palm PC, and any other electronic and processing information device; and

- Control and user interface software.

[0026] This system has the capability to provide the user information on different parameters:

[0027]   a- Production Information:

1- Generator No.

2- Production Lot No.

3- Production Date.

4- Production Control Card.

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[0028]   b- Physical information:

1- Loaded nominal Mo-99 activity.

2- Calibration date and expiration date.

3- Current activity of Mo-99.

4- Hour and date of last elution.

5- Hours elapsed since last elution.

6- Available activity of Tc-99m.

7- Specific activity of Tc-99m expressed in Bq/ng (Ci/ng).

[0029]   c- Radiopharmacologic information:

1- Instruction on how to use, and care for, the Generator, User Location, Other General Recommendations.

2- Available Radiopharmaceuticals for use with the eluate of the Generator.

3- Labeling techniques of cold Radiopharmaceuticals (kits).

4- Quality Control methods of labeled Radiopharmaceuticals

5- Explanatory videos.

6- In the case of the dry Mo-99/Tc-99m generator: the information regarding the residual humidity of the generator is fundamental to secure the next elution, since the elution performance drops drastically in case the generator remains wet. The system guides the user to resolve the problem. If the user fails to log the solution, the generator manufacturer, via internet, may remotely access the data, and call the user to help in resolving the problem.

[0030]   d.- Recordable files: The program records the following parameters:

1- Generator unit number, Lot number, Activity

2- Activity, calibration date, date and timeof system log-in.

3- Date and time of each elution conducted over the life of the generator.

4- Identification code of the operator performing the elution.

5- Eluted activity.

6- Radionucleidic purity of the Tc-99m obtained (mCi Mo-99/mi Tc-99m).

7- Radiopharmaceuticals labeled with the eluted Tc-99m.

8- Comments by the user.

9- Date and time of log-out from the system.

10- Watchdog: alerts the person in charge of the use of the generator: when the system is connected, and this information may be transmitted to a cellular phone, to a text message reception unit, to a pre-selected message box or e-mail inbox via Internet.

11- Search of performance records of all generators data for statistical analysis or any other usage

[0031]   e- Internet Connection: This connection allows the user to obtain information on-line of the following parameters of the generator as these parameters are reported by the manufacturer (sterility and LAL test results are not available for a few days after the generator is shipped to the user):

1- Generator No.

2- Production Lot No.

3- Production Date

4- Production control card.

5- Loaded activity.

6- Calibration date.

7- Quality control card (radiochemical purity, radionucleidicpurity, Sterility, LAL, etc.)

[0032] Furthermore, it allows the producer to obtain information on-line, if access is granted by the user, on the following parameters:

1- Every intervention conducted on the generator.

2- Generator performance.

3- Product use.

4- User profile.

5- Generator traceability during its useful life.

6- Product performance quality in case of discrepancies as to its functioning.

[0033] The user has an on-line message box with the producer for comments or suggestions. Such connection allows the functioning of the watchdog described above.

[0034] The program runs in the background, using minimum PC capacity, while other functions are being used.

[0035] SYSTEM CONFIGURATIONS AND VERSIONS

[0036] Example 1: RadioFarma Elucom I System

This system consists of:

- A classical Mo-99/Tc-99m generator either with a dry or wet column;

- Electronic sensor of elution;

- Communication interface by RS 232; USB, parallel Port or any other input-output port of a PC; and

- User interface software.

[0037] The system is the most economical and practically does not increase the cost of the generator. It retains all the functions mentioned above but due to the lack of the electronic memory. It is necessary to input some data manually, namely, lot and generator numbers, so the rest of the information is electronically exchanged with the producer. It neither measures the eluted activity nor the radionucleidic purity of the Tc-99m eluted.

[0038] Example 2: RadioFarma Elucom II System

[0039] This system consists of:

- The classical Mo-99/Tc-99m generator either with a dry or wet column;

- Electronic sensor of elution;

- On Board Electronic memory with information to the user on: Lot No., Generator no., activity, calibration and expiration dates;

- Communication interface by RS 232; USB, parallel Port or any other input-output port of a PC; and

-User interface software.

[0040] This version enters the corresponding information of the generator connected to the system, which recognizes it as a new generator and allows electronic exchange of information, notifying the producer that the generator is in place and running.

[0041] This version does not measure the eluted activity or the radionucleidic purity of Tc-99m.

[0042] Example 3: RadioFarma Elucom III System

[0043] This system consists of:

- A classical Mo-99/Tc-99m generator either with a dry or wet column;

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- Electronic sensor of elution;

- Electronic memory with information to the user on: Lot No., Generator no., activity, calibration and expiration dates;

- Eluted activity and eluted Tc-99m radionucleidic purity measurement device;

- Communication interface by RS 232; USB, parallel Port or any other input-output port of a PC; and

- User interface software.

[0044] This version, in addition to all other functions described in previous versions, also provides the on-line measurement of the eluted activity and the radionucleidic purity of Tc-99m. The advantage for the user is the automatic recording of the eluted activity and its radionucleidic purity. The advantage for the producer is the on line access to this information to check generator´s performance.

[0045] SYSTEM HARDWARE:

Elution detection method:

[0046] In addition, this invention provides a method for detecting the elution in the generator, which has several practical alternatives already described.

[0047] The sensors used to detect the passage of the liquid through the generator are based on the following physical measurements:

- High-frequency conductometry (most used)

- Optical intensity

- Impedance.

- Capacity

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- Radioactivity

- Magnet-hydrodynamic

[0048] a) High Frequency Conductometry:

It is the method most used and is based on a device having a conductimetric sensor that measures the electrical resistance of a portion of the elution tubing of the generator through which the eluate solution passes. It is clear to those skilled in the art that the conductimetric sensor can be located on other positions of the radioisotope tubings. If the resistance is infinite, it shows that there is no liquid passage and that the column is dry, such condition being ideal for the efficient elution of pertechnetate Tc-99m. A decrease in the electrical resistance, detects the circulating liquid in the elution tubing and the PC logs the moment on which the elution takes place.

[0049] If the resistent does not return to infinite, the program reports that the column has residual moisture; this situation should be reverted by inserting another evacuated vial for the purpose of drying the column. If the situation is not reverted after three attempts to dry the column the program reports a generator malfunction, and suggests calling the manufacturer for technical support.

[0050] b) Optical intensity:

This device, having an optical sensor, measures changes in the intensity of light which passes by a translucid section of the elution tubing. The signal thus generated is processed as in a).

[0051] c) Impedance:

This device, having a free oscillator with a coil over the elution tube, measures the change of the frequency when liquid passes through the elution tube. . The signal thus generated is processed as in a).

[0052] d) Capacity:

This device, having two electrodes over the elution tube, measures the change of the dielectric capacity when liquid passes through the elution tube. A high-frequency capacitive detector interfaced to the PC makes the detection. The signal thus generated is processed as in a).

[0053] e) Activity:

This device measures the activity when the generator is eluted. The measurement may be performed using radioactivity detectors, such as Geiger Müller (GM) tubes, Ionization Chamber, Proportional Detectors, solid state detectors known to those skilled in the art. The elution profile of the Tc-99m is recorded in the system's log, together with the following parameters:

1- That the elution is being performed.

2- The eluted activity of the Tc-99m.

3- The measurement of radioactivity without elution gives the activity of Mo-99 remaining in the generator.

4- The second detector protected by 3 mm of lead allows for the determination of the radiochemical purity of the eluted Tc-99m since it detects the quantity of Mo-99 in the elution. If the ratio μCi Mo-99 per mCi Tc-99m is above the limits established by regulations, the Tc-99m shall be discarded and the information recorded in the system's log.

[0054] f) Magnet-hydrodynamic:

The detection is based on the magnet-hydrodynamic principle, i.e. the generation of a weak orthogonal electric field to the magnetic field applied to the elution pipe of Tc-99m. The measurement of the electric field indicates that the liquid is passing through the interior of the elution tubing.

[0055] PC Connection:

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It is conducted through RS232 since it is a universal port available in every computer. The use of a port USB, RS422, parallel connection, etc., is also provided.

[0056] <u>ON BOARD Memory:</u>

Such memory is present in versions II and III, and is performed through a non-volatile memory such as EEPROM or equivalent. Said memory, upon connecting the system to the PC transfers to the program all the information relating to the generator: Generator Number, Lot Number, Loaded activity, Calibration date, User, etc.

DIGITAL GENERATOR CIRCUITS

[0057] <u>Detection Circuits of liquid passage:</u>

The following circuits are different variants for the detection of elution of the generator, based on the conductometry detection given by the physiological solution that crosses the column of the generator at the moment of the elution. They are based on a high frequency source (in this case it is generated by software and a detection amplifier made up of discreet electronics). The communication is given by port RS232 detailed below, but can be made via parallel port, or USB, or joystick port. The equivalence is indicated in the following table. This equivalence is only worth for this particular case and cannot be taken like between-ports equivalence since each one has its own characteristics.

TABLE

Port RS232				Parallel
Name	function	Pin N° DB9	Pin N° DB25	Pin N°
DCD	In	1	8	11
RXD	In	2	3	12

for U. S. filing**

TXD	Out	3	2	2
DTR	Out	4	20	3
GND	0 volt	5	7	25
DSR	In	6	6	13
RTS	Out	7	4	4
CTS	In	8	5	14
RI	In	9	22	15

[0058] Circuit Number 1: (see Figure 8)

The identification loop acts to knowledge the program that the circuit was connected to the port. This is the simplest circuit and its operation is as follows: by port RTS a voltage pulse is sent. If a stop by port RXD is registered, this indicates that the generator is connected to the computer. If the generator is eluting, the Q1 transistor will be placed in short circuit taking the entering pulse by port RTS to mass, detecting a low point in port RXD. In this way it is detected:

Generator Connected

Generator Eluting

[0059] Circuit N° 2: (see Figure 9)

This circuit works like circuit number 1, but the high pulse entering port RTS loads the capacitor whose load is checked by port DCD. If the generator elutes, Q1 transistor short circuits and discharges the capacitor, being detected from the PC.

[0060] Circuit N° 3: (see Figure 10)

This circuit works by circulation of alternating current by the "needles connection" loop. The alternating voltage is generated by the PC through port RTS. This is checked by port DCD that verifies the connection of the generator. If the generator elutes activity, it is registered by closing the

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"needles connection" loop. This closing produces a short circuit in the Q1 transistor producing a low point in port RXD.

Detection by optical passage:

[0061] Circuit N°4: (see Figure 11)

This circuit acts by changes in the light intensity registered by the phototransistor. This change indicates to the program that the generator is eluting, being registered in the file.

[0062] Circuit N° 5:(see Figure 12)

System of USB connection with data registry for Versions 2 and 3; RadioFarma Elucom II system and RadioFarma Elucom III system.

[0063] The integrated circuit of Cypress Company is a microprocessor with USB connection that makes possible the interface between the detection circuits of liquid passage and the USB port, allowing recording the information mentioned in "Benefits of the Digital Generator". For the RadioFarma Elucom III system the circuit has a digital analogical Interface MAX147 that takes data from radioactivity indicators located in different zones of the Mo99-Tc-99 m Generator.

[0064] Circuits of Radiation monitoring: (see Figure 13)

The RadioFarma Elucom III system has three Geiger Müller-type radiation sensors for measuring the following parameters:

1) Measurement of the remaining Mo-99 activity in the column.

2) Measurement of Tc-99m eluted activity of the generator.

3) Measurement of the radionucleidic purity of the eluted Tc-99m.

[0065] These Geiger's are arranged in the generator in the following way:

[0066] Geiger N°1: It measures the remaining Mo-99 activity in the column. It is positioned on the external face of the lead shield of the generator so that the radiation received comes only from the Mo-99 retained in the column.

[0067] Geiger N°2: It measures the activity of the Tc-99m as it is eluted from the generator. It is located in the Tc-99m exit tubing that carries the eluate from the column. When an elution takes place, the activity that circulates in front of this detector is measured and recorded.

[0068] Geiger N°3: It measures the radionucleidic quality of the eluted Tc-99m. It is located 3mm away from the elution tubing. Between GM N° 3 and the elution tubing there is a 3mm thick lead shield. Enough Mo-99 gamma radiation (740 KeV) crosses this lead shield to be detected and recorded while the Tc-99m gamma radiation (140 KeV) is totally absorbed and not measured by this detector.

[0069] The signals are interfaced to the PC through an 8 channels-12 bits analogical-digital converter, type MAX 147. The data enters the PC via USB port by Cypress C63001 circuit. It is processed by the computer by means of mathematical algorithms giving the following information:

- Remaining Activity of Mo-99 in the column;

- eluted activity of Tc-99m (in case of registering elution);

- Radionucleidic Purity of Tc-99m in μCi of Mo-99/ mCi of Tc-99m; and

- Yield of the generator (in % of Tc-99m actually eluted relative to the theoretical value it should have eluted).